CASE AUTH/1977/3/07

PFIZER v ASTRAZENECA

Statin documents

Pfizer complained about two items on statins which had been supported by AstraZeneca. One was a loose insert in The Pharmaceutical Journal (PJ) of 20 January entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' which stated on the front cover that it was 'Supported by AstraZeneca'. The other was a document entitled 'Prescribing Statins – guidelines as presented by [a named] Primary Care Trust [PCT]' which stated on the front cover 'This leaflet was produced and printed using a grant from AstraZeneca'. AstraZeneca supplied Crestor (rosuvastatin) and Pfizer supplied Lipitor (atorvastatin).

The insert at issue had been the subject of Cases AUTH/1951/2/07 to AUTH/1955/2/07. When the Panel considered Case AUTH/1977/3/07, these cases were to be appealed.

Pfizer alleged that the document published with the PJ might mistakenly be taken to represent the views of NICE (the National Institute for Health and Clinical Excellence). From its appearance readers would assume that this was official NICE guidance and that NICE had stated that Crestor was a cost effective alternative after simvastatin, which was not so. Pfizer alleged that this was misleading and was disguised promotion.

The document contained Crestor material relating to cost efficacy and the Crestor cost model as data on file and a quotation about the safety of Crestor in relation to other statins. Pfizer considered that the selective use of such quotations, as well as the comparison of only Lipitor and Crestor on a cost basis prevented a balanced decision being made.

The document reproduced AstraZeneca promotional graphs and figures. Pfizer alleged that health professionals were likely to be misled as to the nature of the information and the involvement of AstraZeneca; the item was more than 'Supported by AstraZeneca' as claimed on the front page and this lack of clarity was in breach of the Code.

Pfizer considered that the supplement should have contained prescribing information, the statement on adverse event reporting, the AstraZeneca logo and the Crestor brand name.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored/financially supported by AstraZeneca; it had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, at the request of one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control although the choice of some of the material they used was limited to that provided by AstraZeneca.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for Crestor. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of the Code was ruled.

The Panel did not consider that the document looked like official NICE guidance as alleged. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading and disguised in that regard and no breach of the Code was ruled.

The Panel considered that although 'Supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of the Code was ruled.

The Panel noted that given its ruling above that the supplement was, in effect, promotional material for Crestor, it should have included the prescribing information for Crestor which it did not. A breach of

the Code was ruled. The Panel noted that Pfizer had referred to the absence of a statement relating to adverse event reporting but had not cited the relevant clause in its complaint, thus no ruling could be made.

Pfizer had alleged a breach of the requirement that the non-proprietary name of a medicine appear immediately adjacent to the most prominent display of the brand name. The supplement only ever referred to rosuvastatin. There thus could be no breach of the Code and the Panel ruled accordingly.

The NICE guidance on statins recommended that when patients were first treated with a statin they should receive one with a low acquisition cost. Based on this guidance generic simvastatin would be the first choice. If patients failed to reach agreed targets on generic simvastatin they could then be switched to a more expensive statin. The Panel noted, however, that the cost data presented in the supplement, even under the heading 'Calculating the cost of implementing NICE guidance across a primary care trust population', only compared the cost of atorvastatin and rosuvastatin. There was no mention of the cost of generic simvastatin; without this data the Panel considered that it was impossible for readers to fully understand the cost implications of using a second-line statin. The data was misleading and breaches of the Code were ruled.

A cost-effectiveness model was presented in the supplement which featured two tables of data detailing the financial implications of using atorvastatin or rosuvastatin as second-line therapy to simvastatin. Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor summary of product characteristics (SPC), in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. The SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The section on optimizing statin treatment strategies dismissed the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins; it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The supplement was misleading with regard to the safety profile of Crestor and its comparison with other statins and breaches of the Code were ruled.

In relation to the PCT guidelines, Pfizer noted that the statin algorithm recommended using simvastatin first line up to 80mg followed by the most cost effective choice, aiming for treatment targets of total cholesterol <4mmol/L and LDL-C <2mmol/L in secondary prevention and high risk primary prevention. The efficacy and cost efficacy data presented should therefore reflect this algorithm.

However, the cost efficacy argument presented did not reflect the algorithm. The cost per 1% LDL-C reduction table highlighted rosuvastatin 5mg or 10mg as being 'the most cost effective choice after simvastatin'. However, the algorithm recommended titrating simvastatin to 80mg/day before switching therapy. The bar chart on page two showed that patients not treated to target on simvastatin 80mg would require rosuvastatin doses >20mg to obtain further efficacy. The cost efficacy of the 5mg and 10mg doses was therefore not relevant if doses with greater efficacy were required according to the algorithm.

Secondly, the PCT guidelines recommended targets of total cholesterol <4mmol/L and LDL-C <2mmol/L for secondary prevention and high risk primary prevention. A cost efficacy argument needed to consider how many patients could achieve these targets by using rosuvastatin rather than atorvastatin after simvastatin 80mg. Again, the cost per 1% LDL-C reduction as a measure of cost efficacy was not relevant in this clinical scenario where doses of rosuvastatin higher than 5mg or 10mg might be required to achieve these lower targets in patients where simvastatin 80mg had failed.

The LDL-C efficacy data presented were taken from the STELLAR trial. This trial did not include rosuvastatin 5mg but the 5mg dose was discussed in the cost-efficacy section. Pfizer noted that for several patient groups the recommended start dose was 5mg, even when switching from other statins.

On the final page the chart highlighted simvastatin 40mg, rosuvastatin 10mg and atorvastatin 40mg/80mg and encouraged the reader to compare costs. However, these doses had different efficacy and again this did not relate to the algorithm. The 5mg dose of rosuvastatin was missing as was pravastatin 40mg.

Pfizer noted the supplementary information to the Code that economic evaluation must be consistent with the product's marketing authorization. Pfizer considered that failure to discuss the dosing limitations of rosuvastatin that would be likely to be relevant following the treatment failure of simvastatin 80mg, conflicted with this aspect of the Code.

No safety data relating to any of the medicines discussed were presented. As well as preventing the formation of a balanced opinion, Pfizer alleged this was in breach of the Code, which required an unbiased and balanced view of the risk/benefit ratio of any treatment.

The data presented, the references quoted and the cost effectiveness model used focussed on AstraZeneca material, and indeed many of the graphs were taken directly from Crestor promotional material. The front of the document should therefore clearly have stated that this item was not just supported by a grant from AstraZeneca, but was written in collaboration with it and the absence of such a statement breached the Code.

Pfizer understood the document had been used by AstraZeneca's representatives in meetings with health professionals and as such prescribing information for rosuvastatin was needed.

In relation to the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect on health but would save £1.1 billion over five years' (Moon and Bogle 2006), Pfizer noted that many of the assumptions made in the cost-model used by Moon and Bogle were still debated. As such, Pfizer alleged that the quotation was unbalanced and misleading, and that it disparaged atorvastatin.

Finally, the document appeared to be PCT guidance representing that PCT's opinion. However, it was clear that AstraZeneca had had considerable involvement in its preparation. This could mislead a health professional as to the nature and source of the document and represented disguised promotion.

The Panel noted that the document had been produced and printed using a grant from AstraZeneca; it had been co-developed by AstraZeneca and the PCT. It was used by representatives, within a Crestor promotional call, as an aid to discussing the PCT's statin guidelines. AstraZeneca had thus used the document in a promotional context. The Panel also noted AstraZeneca's submission that the item was used incorrectly during a promotional call. The Panel noted that as the document referred to rosuvastatin, and made several claims for the product, the balance of probabilities was that representatives, in a Crestor promotional call, would have used the document for a promotional purpose. Given the company's creation of the document and subsequent use of it, the Panel considered that it was, in effect, promotional material for Crestor that had been disguised; the document appeared to be the independent PCT guidelines produced and printed using a grant from AstraZeneca. In that regard the Panel noted that the PCT logo was more prominent than the statement relating to AstraZeneca's support. A breach of the Code was ruled.

The Panel considered that the phrase 'This leaflet was produced and printed using a grant from AstraZeneca' gave misleading details about the company's role. A breach was ruled as acknowledged by AstraZeneca.

As the document did not include prescribing information for Crestor, a breach was ruled as acknowledged by AstraZeneca.

AstraZeneca did not answer Pfizer's allegations regarding the content of the document, although it disagreed that any content was factually incorrect or that it disparaged atorvastatin. The Panel noted that the document had been approved by AstraZeneca's signatories.

The Panel had no information about the algorithm other than that given in the document. Page 1 referred to secondary prevention target/high risk primary prevention giving targets of less than 4 for total cholesterol and LDL-C less than 2 or total cholesterol reduction of 25% and LDL-C reduction of 30% - whichever was greater. The primary prevention targets were total cholesterol less than 5 and LDL-C less than 2.5. The data on pages 2 and 3 of the document referred only to percentage reduction in LDL-C. Thus the efficacy and cost data did not reflect the algorithm. The Panel ruled that the document was misleading in this regard in breach of the Code.

A bar chart compared the percentage reduction in LDL-C from baseline for simvastatin (10-80mg), rosuvastatin (10-40mg) and atorvastatin (10-80mg). It appeared that if a greater percentage reduction was required than was possible with simvastatin 80mg (approximately -45%) then patients would have to receive either rosuvastatin (20 or 40mg) or atorvastatin (40 or 80mg). This was followed by the Moon and Bogle quotation then the claim 'Rosuvastatin, at a start dose of 5 or 10mg, is the most cost effective choice after simvastatin'. Given the content of the bar chart and the positioning of the claim the Panel considered that the claim was misleading as the cost efficacy of the 5mg and 10mg doses was irrelevant given that usually higher doses would be needed. In addition the bar chart did not give any indication of the LDL-C reduction from baseline for the 5mg dose. A breach of the Code was ruled.

Below the claim were two tables of data showing the cost per 1% LDL-C reduction for rosuvastatin (5-40mg) and atorvastatin (10-80mg). It was stated that the cost was based on pack sizes of 28 tablets. Given that the cost of 28 x 40mg rosuvastatin was £29.69 and it lowered LDL-C from baseline by 55% the cost per percentage LDL-C reduction was stated as 53 pence. This cost, however, took no account of the fact that the SPC recommended specialist supervision when the 40mg dose was initiated. Further 40mg should only be used in high risk patients in whom routine follow-up would be performed. Such follow-up would add to the cost of therapy. In that regard the Panel ruled that the data were misleading in breach of the Code.

The bar chart which compared the percentage reduction in LDL-C from baseline showed results for rosuvastatin 10mg, 20mg and 40mg. It thus appeared that the lowest dose of rosuvastatin was 10mg which was not so. A 5mg dose was available which, according to the Crestor SPC, was recommended in some patients. Although a footnote to the bar chart stated 'For recommended start and maximum doses

for individual patients, please refer to SmPC', this did not negate the otherwise misleading impression with regard to the availability of doses. A breach of the Code was ruled.

A cost comparison chart was on a page headed 'Prescribing statins' with a subheading 'Lipid Lowering Drugs – cost comparison'. The chart gave the cost for 28 days' treatment of a number of lipid lowering agents and highlighted three - simvastatin 40mg (£3.89), rosuvastatin 10mg (£18.03) and atorvastatin 40mg, 80mg (£28.21). The Panel noted that, according to the bar chart on the previous page which showed the percentage reduction in LDL-C from baseline, simvastatin 40mg would lower LDL-C by up to approximately -38%, rosuvastatin by up to -45% and atorvastatin 80mg by up to -50%. In terms of LDL-C lowing efficacy these three agents were thus not equivalent. The Panel considered, however, by highlighting these three medicines/doses, readers would assume that they were therapeutically equivalent which was not so. The footnote 'Doses given do not imply therapeutic equivalence' did not negate the impression given. A breach of the Code was ruled.

The cost comparison chart was not limited to statins; it was unclear as to the basis on which products had been chosen. Rosuvastatin had been included at doses of 10mg, 20mg and 40mg but not at 5mg. Pravastatin was included but only at a dose of 20mg although the recommended dose range was 10-40mg. The basis of the cost comparison was unclear and was thus misleading in breach of the Code.

The quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect no health but would save £1.1bn over five years…' was referenced to Moon and Bogle. Pfizer had submitted that there had been some debate about the authors' assumptions but it had not provided any detail. There was no response from AstraZeneca. Nonetheless the Panel considered that not everyone who currently took 20mg atorvastatin would be suitable to change to simvastatin 40mg. In that regard the Panel noted that the percentage reduction in LDL-C from baseline for the two products was shown as approximately -41% and -38% respectively. Thus some patients on atorvastatin 20mg might fail to reach lipid targets if they were switched to simvastatin 40mg. On the information provided the Panel considered that although the short quotation from Moon and Bogle might be misleading it did not disparage atorvastatin as alleged; no breach was ruled.

The Panel ruled a breach as the document failed to present a balanced view of the risk/benefit ratio of any treatment as alleged.

Pfizer also alleged that the degree of potential confusion over the true content of the two items, the similarity of the breaches and the short time-period over which they were produced suggested consistent shortfalls within AstraZeneca.

The Panel noted that AstraZeneca had failed to recognise that the document placed in the PJ was, in effect, promotional material for Crestor. Similarly the PCT guidelines had been entered into the company's copy approval system in such a way that the intent of the originator had either not been apparent or had been misinterpreted by the signatories. The Panel considered that such flaws in the copy approval system, highlighted by the generation of both documents, were unacceptable. High standards had not been maintained. A breach of the Code was ruled.

The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in both documents, neither referred to the requirements in the SPC with regard to the specialist supervision and routine patient follow-up. The Panel considered that the omission of such information might prejudice patient care. The two documents had brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted its rulings above and decided, in accordance with Paragraph 7.1 of the Constitution and Procedure, that if there was subsequently an appeal by AstraZeneca relating to the PCT guideline it would require AstraZeneca to suspend the use of the document pending the final outcome. The supplement from the PJ was already the subject of a forthcoming appeal.

The Panel considered that this case highlighted an apparent lack of control in AstraZeneca's copy approval system. Furthermore the Panel was extremely concerned that when it had asked the company for further information about the PCT guidelines AstraZeneca had submitted that it had now had the opportunity to undertake a full investigation into this complaint. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007. AstraZeneca's second response to the Authority differed markedly from the first. This was unacceptable. Self-regulation depended upon companies investigating matters fully at the outset and submitting full and frank responses both in inter-company correspondence and to the Authority. The Panel also noted AstraZeneca's dismissal of questions relating to the content of the PCT guidelines document.

Overall, the Panel was extremely concerned about AstraZeneca's procedures with regard to the Code including its incorrect initial responses and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that AstraZeneca had accepted all of the rulings regarding the piece which had been distributed with the PJ; rather than being a sponsored supplement, as described by AstraZeneca, the Appeal Board had decided in Cases AUTH/1951/2/07 to AUTH/1955/2/07 that the piece was a paid for promotional insert for Crestor. The

Appeal Board noted that it would consider the report on the basis of the information before it in the present case (Case AUTH/1977/3/07).

The Appeal Board noted that AstraZeneca's erroneous belief that the PCT guidelines was a PCT-generated document was solely based upon a verbal communication from the relevant medical signatory. The Appeal Board was concerned that there had been no follow up investigation or documentation sought which would have shown the communication was untrue. The Appeal Board also noted AstraZeneca's submission that there was inadequate communication between the field and head office about the document. The Appeal Board was concerned that AstraZeneca had responded to both Pfizer in its inter-company correspondence and then to the Authority in its initial response to the complaint without adequate investigation. This was totally unacceptable. There was no documentation in the job bag to support PCT involvement with the generation of the guidelines. It appeared that only upon investigation of a request for further information by the Panel did AstraZeneca discover that its initial response was incorrect and so informed the Authority.

AstraZeneca had stated that the PCT guidelines had been withdrawn on 1 March. However, the Appeal Board noted that an email timed at 16:36 on 1 March highlighted the requirements of the Code relevant to the delivery of the item but allowed continued use. The Appeal Board noted from AstraZeneca that despite this permitted use, due to continuing confusion about the item's use, it had not been used beyond 1 March. The Appeal Board was concerned that the process for withdrawal of the item was uncertain. An email permitting use could not amount to effective withdrawal of use.

The Appeal Board noted that AstraZeneca accepted that errors had been made for which it apologised and provided details of corrective action taken.

The Appeal Board considered that effective and robust self-regulation relied upon companies making fully informed responses to complaints. AstraZeneca had not made sufficient investigations and as a result it had provided incorrect responses which was totally unacceptable. The Appeal Board considered this matter to be of the utmost seriousness.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of AstraZeneca's procedures in relation to the Code to be carried out by the Authority. In addition the Appeal Board decided, on the basis that it had not fully investigated the matter of the PCT guidelines when it responded to Pfizer and in its first response to the Authority, that AstraZeneca should be publicly reprimanded.

Upon receipt of the audit report, the Appeal Board considered that AstraZeneca should provide the Authority with a copy of its new standard operating procedures (SOPs). On the basis that the SOPs were provided and that the recommendations from the audit report were implemented the Appeal Board decided that no further action was required.

Pfizer Limited complained about two items on statins which had been supported by AstraZeneca UK Limited. One was a supplement to The Pharmaceutical Journal of 20 January entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' which stated on the front cover that it was 'Supported by AstraZeneca'. The other was a document (ref CRES10213) entitled 'Prescribing Statins – guidelines as presented by [a named] Primary Care Trust [PCT]' which stated on the front cover 'This leaflet was produced and printed using a grant from AstraZeneca'.

AstraZeneca supplied Crestor (rosuvastatin) and Pfizer supplied Lipitor (atorvastatin).

1 Insert on statins in The Pharmaceutical Journal

The material had been the subject of Cases AUTH/1951/2/07 to AUTH/1955/2/07. When the Panel considered Case AUTH/1977/3/07, these cases were to be appealed.

COMPLAINT

Pfizer stated that the insert put forward opinions which might mistakenly be taken to represent the views of NICE (the National Institute for Health and Clinical Excellence), considering their presence in a review of NICE guidance. From its appearance the reader might assume that this was official NICE guidance and that NICE had stated that Crestor was a cost effective alternative after simvastatin, which was not so. Pfizer alleged that this was misleading and was disguised promotion in breach of Clause 10.1 of the Code.

Inside there was one page on NICE guidance on statins and the majority of the rest of the document contained Crestor material relating to cost efficacy and the Crestor cost model as data on file. The safety section included a quotation about the safety of Crestor in relation to other statins. Pfizer considered that the selective use of such quotations, as well as the comparison of only Lipitor and Crestor on a cost basis prevented a balanced decision being made on the basis of this material. Pfizer alleged breaches of Clauses 7.2 and 7.3.

The item reproduced AstraZeneca promotional graphs and figures. Pfizer alleged that the presentation of the piece was likely to mislead health professionals as to the nature of the information contained within and the involvement of AstraZeneca in its preparation in breach of Clause 10.1.

As a result of the inclusion of material lifted from Crestor promotional material and the use of cost models prepared by AstraZeneca, Pfizer considered this piece was certainly more than 'Supported by AstraZeneca' as claimed on the front page and alleged

that this lack of clarity concerning the company's involvement was in breach of Clause 9.10.

Given the above, Pfizer considered that the supplement was a promotional item and thus should have contained prescribing information, the usual statement on adverse event reporting, the AstraZeneca logo and the Crestor brand name. All of these were missing, in breach of Clauses 4.2 and 4.3.

The perception that this whole document could be misinterpreted as a commentary on official NICE guidance and that all the Crestor promotional material was part of the NICE guidance Pfizer considered was very serious. Indeed, Pfizer questioned whether this could be described as a NICE-related summary at all, as the majority of the text and tables related to promotion of Crestor's cost-benefit ratio, with only a limited discussion of the findings of the NICE statin guidance.

RESPONSE

AstraZeneca submitted that the supplement in question was distributed with The Pharmaceutical Journal on 20 January and written by a GP and a pharmacist and was financially supported by AstraZeneca; a sponsorship statement 'Supported by AstraZeneca' appeared on the front cover.

The supplement was developed in 2006. AstraZeneca was told that the supplement was going to be published in January 2007, however the company only became aware that it had been distributed when it was raised in discussion between a pharmacist and a member of its medical team. Subsequently, five letters of complaint appeared in The Pharmaceutical Journal and these were the subjects of Cases AUTH/1951/2/07 to AUTH/1955/2/07.

The editorial board of The Pharmaceutical Journal responded in a leading article entitled, 'We call this free speech' which clearly presented its views on the nature and purpose of the supplement. In addition, the authors had published their responses to the readers' comments. The journal had not invited AstraZeneca to comment.

During its regular discussions with health professionals AstraZeneca became aware that they were unclear as to how the recommendations published in the NICE Statin Technology Appraisal in early 2006 should be implemented, taking into consideration seemingly conflicting advice from different sets of guidelines.

The initiation of the supplement arose out of awareness of this issue. AstraZeneca's agency asked if The Pharmaceutical Journal would be interested in such an educational discussion article and when the journal confirmed that it was, the agency contacted two of the health professionals who had previously identified the issue and were interested to co-develop an outline for the article. AstraZeneca was aware of the outline and the health professionals' input to this. These health professionals were well-respected, independent medical authors who frequently contributed articles to the medical press. The two authors wrote the article themselves and had full editorial control. The GP requested the cost-effectiveness tables and information from AstraZeneca's data on file and reviewed the content. As required by the Code, AstraZeneca reviewed the document to ensure that it was factually correct and did not contravene the Code or the relevant statutory requirements. Other than this, the authors had full editorial control and the views expressed therein. Prior to publication, The Pharmaceutical Journal reviewed the supplement to ensure it met editorial standards. The supplement had not been distributed by other means.

AstraZeneca submitted that the supplement did not present itself as an official NICE document; no Department of Health (DoH) or NICE logos appeared anywhere. Furthermore, the appropriate declaration of sponsorship from AstraZeneca, as required by the Code, was on the front cover. The full title of the document, 'The new NICE guidance on the use of statins in practice - Considerations for implementation', made it clear that this was a review of issues and considerations surrounding the NICE guidance rather than any official document from NICE itself.

AstraZeneca noted that the first chapter of the review was entitled 'The NICE guidance recommendations' and, as the title implied, described NICE's recommendation. The second chapter, 'The UK cholesterol story', put the guidance into the context of other guidelines in this therapeutic area such as the National Service Framework on Coronary Heart Disease, European Atherosclerosis Society guidelines and the Joint British Societies' 2005/06 guidance. As no statin was mentioned by name in either of these two sections, it was difficult to understand how Pfizer had construed this article as intentionally implying that NICE had endorsed any of the currently available UK statins. AstraZeneca therefore denied a breach of Clause 10.1.

AstraZeneca noted that the third chapter of the supplement was entitled 'Reaching targets by optimising statin treatment strategies'. The company considered that the title clearly differentiated this section from NICE's opinions.

AstraZeneca disagreed that the supplement was intended to be or could be considered to be promotional. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency sought prior confirmation that this would be an interesting and valid educational topic for readers of The Pharmaceutical Journal and commissioned two writers, who were independent of AstraZeneca, to write the article. AstraZeneca sponsored the supplement, was aware of its proposed outline and reviewed it in accordance with Code requirements to check that the content was not promotional and the information was accurate and balanced.

The supplement introduced data comparing the efficacy of the four leading UK statins, based on Jones *et al* (2003). Although this was an AstraZeneca study, it was the only head-to-head comparative trial of the four most widely prescribed UK statins. Therefore its inclusion was extremely relevant in a supplement which attempted to offer health professionals guidance on choosing statin options in the management of dyslipidaemia and was consistent with the need to consider a fair representation of the balance of available evidence.

With regard to Pfizer's comments relating to safety issues, AstraZeneca noted that many health professionals continued to refer to regulatory concerns about the statin class as a result of the cerivastatin withdrawal in 2001 and the activities of Public Citizen, a US consumer group that ran a sustained multimedia campaign against Crestor following the product's launch. This had led to inappropriate negative safety perceptions about the product that the authors felt could be partly addressed in this article.

In response to this campaign and other issues around statin safety both the Food and Drug Administration (FDA) and the US National Lipid Association (NLA) had published reports confirming that all the currently available statins had similar safety profiles. The lengthier NLA report was quoted twice by the authors. Neither quotation mentioned any specific product but referred to statins having comparable safety profiles or similar. The authors chose to put the NLA report into the context of Public Citizen's campaign by mentioning the product in the introduction to these quotations.

As the only statin safety statement was one of parity across currently available [statins] and the only mention of rosuvastatin (Crestor) was relevant in this context AstraZeneca did not consider that this constituted a claim for superior safety or, in this context, any other potential breach of the Code as implied by Pfizer. AstraZeneca thus denied breaches of Clauses 7.2 and 7.3.

AstraZeneca acknowledged that figures and graphs produced by it were included in the supplement. These were provided following the authors' request for illustrations of the data referred to in the article. AstraZeneca exerted no influence on the choice of data or the graphs and figures used to illustrate the information presented. These choices were entirely those of the authors. AstraZeneca ensured that there was no visible branding on any of the items provided for the authors' consideration and ensured that the figures used looked significantly different from similar information presented in Crestor promotional materials. AstraZeneca denied a breach of Clause 10.1.

For the reasons already stated, AstraZeneca disagreed with Pfizer's view that the supplement was intended to be or could be considered to be a promotional item. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The two authors were independent of AstraZeneca. AstraZeneca sponsored the supplement, knew of the proposed outline and reviewed the supplement in accordance with Code requirements to check that the content was accurate and balanced.

Industry support for such independently written review articles was a legitimate means of providing education and debate for health professionals. AstraZeneca believed that the supplement provided valid, unbiased and appropriate educational content and topical discussion and had been produced in accordance with both the spirit and letter of the Code. AstraZeneca aimed to maintain high standards in all aspects of its internal review process as well as wishing to support respected sources of information and education for health professionals. AstraZeneca did not accept that there had been a breach of Clause 9.10.

Prescribing information and other requirements for promotional items had not been included in the supplement as it was a review article written by two independent health professionals, not a promotional item written by AstraZeneca. The information that it contained was the opinion of the independent authors and any information relating to rosuvastatin (Crestor) was presented in a balanced, factual and accurate manner taken from peer reviewed publications or publicly available documents (with the exception of the cost-effectiveness data which was supplied by AstraZeneca on request). There were no claims within this article that promoted the prescription, supply, sale or administration of Crestor. As indicated in the editorial comment in The Pharmaceutical Journal, the journal's editors also did not consider it to be promotional in nature. AstraZeneca did not therefore accept that there had been breaches of Clauses 4.2 and 4.3.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored/financially supported by AstraZeneca. The supplement had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The

supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control although the choice of some of the material they used was limited to that provided by AstraZeneca.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for AstraZeneca's product Crestor. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of Clause 10.1 was ruled.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not have the appearance of official NICE guidance as alleged. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading and disguised in that regard and no breach of Clause 10.1 was ruled.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel considered that although the phrase 'Supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of Clause 9.10 was ruled.

The Panel noted its ruling above that the supplement was, in effect, promotional material for Crestor. The supplement should thus have included the prescribing information for Crestor which it did not. A breach of Clause 4.1 was ruled. The Panel noted that Pfizer had referred to the statement relating to adverse event reporting. The requirement to include this statement in promotional material was contained in Clause 4.10 of the Code. As Pfizer had not cited Clause 4.10 in its complaint, the Panel could make no ruling in this regard but asked that AstraZeneca be advised of its concerns.

The Panel further noted that Pfizer had alleged a breach of Clause 4.3. Clause 4.3 required, *inter alia*, the non-proprietary name of a medicine to appear immediately adjacent to the most prominent display of the brand name. The supplement at issue did not contain any reference to Crestor – the medicine was only ever referred to as rosuvastatin. There thus could be no breach of Clause 4.3 and the Panel ruled accordingly.

The Panel noted that the NICE guidance on statins recommended that when patients were first treated with a statin they should receive one with a low acquisition cost. Based on this guidance generic simvastatin would be the first choice. If patients failed to reach agreed cholesterol targets on generic simvastatin they could then be switched to a more expensive statin. The Panel noted, however, that the cost data presented in the supplement, even under the heading 'Calculating the cost of implementing NICE guidance across a primary care trust population' only compared the cost of atorvastatin (Pfizer's product, Lipitor) and rosuvastatin (Crestor). There was no mention of the cost of generic simvastatin; without this data the Panel considered that it was impossible for readers to fully understand the cost implications of using a second-line statin. In that regard the Panel considered that the data was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that a cost-effectiveness model was presented in the supplement which featured two tables of data detailing the financial implications of using atorvastatin or rosuvastatin as second-line therapy to simvastatin. Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor summary of product characteristics (SPC), in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading with regard to the safety profile of Crestor and its comparison with other statins. Breaches of Clauses 7.2 and 7.3 were ruled.

2 PCT Prescribing Statins guidelines document

COMPLAINT

Pfizer noted that the PCT statin algorithm recommended using simvastatin first line up to 80mg (as 2 x 40mg) followed by the most cost effective choice, aiming for treatment targets of total cholesterol <4mmol/L and LDL-C <2mmol/L in secondary

prevention and high risk primary prevention. The efficacy and cost efficacy data presented should therefore reflect this algorithm.

However, the cost efficacy argument presented did not reflect the algorithm. The cost per 1% LDL-C reduction table highlighted rosuvastatin 5mg or 10mg as being 'the most cost effective choice after simvastatin'. However, the algorithm recommended titrating simvastatin to 80mg/day before switching therapy. The bar chart on page two showed that patients not treated to target on simvastatin 80mg would require rosuvastatin doses >20mg to obtain further efficacy. The cost efficacy of the 5mg and 10mg doses was therefore not relevant if doses with greater efficacy were required according to the algorithm.

Secondly, the PCT guidelines recommended targets of total cholesterol <4mmol/L and LDL-C <2mmol/L for secondary prevention and high risk primary prevention. A cost efficacy argument needed to consider how many patients could achieve these targets by using rosuvastatin rather than atorvastatin after simvastatin 80mg. Again, the cost per 1% LDL-C reduction as a measure of cost efficacy was not relevant in this clinical scenario where doses of rosuvastatin higher than 5mg or 10mg might be required to achieve these lower targets in patients where simvastatin 80mg had failed.

The LDL-C efficacy data presented were taken from the STELLAR trial. This trial did not include rosuvastatin 5mg but the 5mg dose was discussed in the cost-efficacy section. Pfizer noted that for several patient groups (elderly >70 years, patients with moderate renal impairment, patients with risk factors for myopathy and patients of Asian origin) the recommended start dose was 5mg, even when switching from other statins.

On the final page the chart highlighted simvastatin 40mg, rosuvastatin 10mg and atorvastatin 40mg/80mg and encouraged the reader to compare the costs of these. However, these doses had different efficacy and again this did not relate to the algorithm. The 5mg dose of rosuvastatin was missing from the chart as was pravastatin 40mg.

Pfizer alleged that these shortcomings represented a breach of Clause 7.2. Pfizer noted the supplementary information to Clause 7.2 on the economic evaluation of medicines, which stated that economic evaluation must be consistent with the product's marketing authorization. Pfizer considered that failure to discuss the dosing limitations of rosuvastatin that would be likely to be relevant following the treatment failure of simvastatin 80mg, conflicted with this aspect of the Code.

It should also be noted that no safety data relating to any of the medicines discussed were presented. As well as preventing the formation of a balanced opinion based on the information in the document, Pfizer believed this was in breach of Clause 7.10, which required that promotional material clearly represented an unbiased and balanced view of the risk/benefit ratio of any treatment.

The data presented, the references quoted and the cost effectiveness model used were very focussed on AstraZeneca material, and indeed many of the graphs were taken directly from Crestor promotional material, differing only in the absence of the Crestor colour coding. The wording on the front of the leaflet should therefore have clearly stated that this item was not just supported by a grant from AstraZeneca, but was written in collaboration with it. Pfizer alleged the absence of such a statement breached Clause 9.10.

Pfizer understood the document had been used by AstraZeneca's representatives in meetings with health professionals ie it was being used as a promotional piece and as such must have prescribing information for rosuvastatin firmly attached, as stated in Clause 4.1. It was therefore in breach of Clause 4.1.

The document contained the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect on health but would save £1.1 billion over five years' (Moon and Bogle 2006). In relation to this, Pfizer noted the supplementary information to Clause 7.2 which stated 'Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. As highlighted in a letter to the BMJ (Lloyd 2006), debate still existed concerning many of the assumptions made in the cost-model used by Moon and Bogle. As such, Pfizer alleged that a single statement taken from this editorial was unbalanced and misleading, and that it disparaged atorvastatin in breach of Clause 8.1.

Finally, viewed as a stand-alone item, the document appeared to be guidance which was written by the PCT and which represented an opinion which it itself had formed. However, considering that the focus was solely on rosuvastatin data and Crestor promotional material, it was clear that AstraZeneca had had considerable involvement in its preparation. This could mislead a health professional as to the nature and source of the material they were receiving and represented disguised promotion in breach of Clause 10.1.

RESPONSE

When asked by the Panel for further information following consideration of its initial response, AstraZeneca submitted a wholly new response to this part of Pfizer's complaint. The company submitted that it had now undertaken a full investigation into this complaint, including conversations with the relevant personnel. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007.

AstraZeneca explained that following a change of local policy the PCT distributed its guidelines within the 'Statin Special' Prescribing Newsletter of March 2006.

Through subsequent conversations between AstraZeneca and the PCT, AstraZeneca became aware that the PCT was willing to discuss support that AstraZeneca could provide in dissemination of the guidelines messages to local GPs. It was subsequently agreed that AstraZeneca would support the PCT by distributing the content of its lipid guidelines by creating a bespoke item.

The item was then co-developed by AstraZeneca and the PCT. The final wording and layout was approved by the PCT. Discussions between field and head office personnel at that stage, acknowledged the fact that the item would require AstraZeneca's approval. The item was then entered in the internal AstraZeneca review process and approved for use.

The signatories reviewed the item on the understanding that it was a document created by the PCT, for which AstraZeneca paid for the production and printing under Clause 18.4. However, it became apparent before the final item production that the intent was for representatives to distribute the item. In the initial investigation, AstraZeneca understood that guidance was given verbally to the relevant AstraZeneca field personnel when the item became available for use, advising how it should be used in order to ensure that it was delivered as a service to medicine within the requirements of the Code.

Following Pfizer's allegation that AstraZeneca representatives were using the item within a promotional call, the relevant managers were contacted and both verbal and written clarification was restated on how the item should be used. Pfizer was unable to provide evidence that the item had been used to promote Crestor and at that time AstraZeneca did not think that the item was being used to promote Crestor.

AstraZeneca had now investigated further. In its opinion, both the nature of AstraZeneca's involvement in the item and the intent of how the item would be used were not interpreted in the same way by the originator and the final signatories from the outset. This misunderstanding had led to subsequent confusion of implementation. Whilst the intent of the originator was for the item to be used by the sales teams to support the PCT guidelines, the level of involvement that had already taken place prior to the item being entered into the approval system was not evident to the signatories. Additionally, upon approval of the item the requirements relating to the method of final distribution were not made explicit from head office back to the field team, as the company had originally understood to be the case.

It appeared that the verbal guidance from head office to the field that should have taken place when the item was delivered to the sales team did not happen. The sales manager and the original AstraZeneca contact with the PCT, believing that they were delivering a legitimately approved item, advised the local AstraZeneca representatives (approximately three at that time) that, should the doctor raise the local guidelines in a call then this item could be used in the discussion, with the support of the PCT. The item was therefore used as a discussion aid for the PCT guidelines within a promotional call for Crestor. AstraZeneca had no evidence to believe that Crestor was promoted from this item.

In response to the concerns raised by Pfizer, since AstraZeneca believed that this item was being approved for use as a service to medicine, it was not considered appropriate for the company to comment on the data therein that represented the PCT's guidelines. The additional data that was included in the item but which did not appear in the PCT Newsletter, had informed the original guideline recommendation as indicated on the front page of this item. AstraZeneca did not input into the writing of the PCT guidelines, therefore the company did not consider it was appropriate for it to answer Pfizer's criticism of the content and the scientific rationale behind it. AstraZeneca also disagreed that there was any content that was factually incorrect or that could be construed as disparaging to atorvastatin.

AstraZeneca accepted that the sponsorship statement did not accurately reflect the funding of this item, as no grant was given to the PCT during this collaboration. AstraZeneca paid for the layout and printing of the item. Therefore it acknowledged a breach of Clause 9.10.

AstraZeneca also acknowledged that since this item was incorrectly used within a promotional call, and because AstraZeneca has some involvement in the creation of the item, as it did not include prescribing information it breached Clause 4.1. However, since the brand name 'Crestor' did not feature in the item, it refuted that there was any case to answer in relation to Clause 4.3.

AstraZeneca's investigation suggested that this was an isolated incident occurring only within the one area, due to a combination of factors, which included the fact that this type of collaboration to communicate guidelines had not occurred before and the inexperience of the individuals involved. AstraZeneca also believed strongly that the original intent to provide support, via the local sales team, to the PCT was legitimate. On receiving the Pfizer inter-company complaint, action was taken with a prompt re-briefing issued to the field teams and subsequently to relevant team members. Use of the item ceased whilst the investigation was taking place. In light of this complaint the PCT personnel had been contacted and would be informed of the content of its response. AstraZeneca had already started to develop a policy for the correct procedures for co-development of such materials in full compliance with Clause 18.4.

In conclusion AstraZeneca believed there was a clear miscommunication and a lack of clarity between its field force and head office which warranted rulings of a breach of Clauses 4.1 and 9.10. AstraZeneca was grateful that this matter was brought to its attention so that it could take the steps outlined in this letter to prevent any such future misunderstandings.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The document in question had been produced and printed using a grant from AstraZeneca; it had been co-developed by AstraZeneca and the PCT. The document was used by representatives, within a Crestor promotional call, as an aid to discussing the PCT's statin guidelines. AstraZeneca had thus used the document in a promotional context. The Panel also noted AstraZeneca's submission that the item was used incorrectly during a promotional call. The Panel noted that as the document referred to rosuvastatin, and made several claims for the product, the balance of probabilities was that representatives, in a Crestor promotional call, would have used the document for a promotional purpose. Given the company's creation of a bespoke document and subsequent use of it, the Panel considered that it was, in effect, promotional material for AstraZeneca's product, Crestor. The Panel considered that it was disguised promotion in that the document appeared to be the independent PCT guidelines produced and printed using a grant from AstraZeneca. In that regard the Panel noted that the PCT logo was more prominent than the statement relating to AstraZeneca's support. A breach of Clause 10.1 was ruled.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The Panel considered that the phrase 'This leaflet was produced and printed using a grant from AstraZeneca' gave misleading details about the company's role. A breach of Clause 9.10 was ruled as acknowledged by AstraZeneca.

The Panel noted its ruling above that the document was, in effect, promotional material for Crestor. The supplement should thus have included the prescribing information for Crestor which it did not. A breach of Clause 4.1 was ruled as acknowledged by AstraZeneca.

The Panel noted that, in response to Pfizer's allegations regarding the content of the document, AstraZeneca had stated that it did not consider it appropriate for the company to answer such allegations. AstraZeneca, however, disagreed that there was any content that was not factually correct or that could not be construed as disparaging to atorvastatin. The Panel noted that the document had been approved by AstraZeneca's signatories.

The Panel noted that it had no information about the PCT algorithm other than that given in the document at issue. Page 1 referred to secondary prevention target/high risk primary prevention giving targets of less than 4 for total cholesterol and LDL-C less than 2 or total cholesterol reduction of 25% and LDL-C reduction of 30% - whichever was greater. The primary prevention targets were total cholesterol less than 5 and LDL-C less than 2.5. The data on pages 2 and 3 of the document referred only to percentage reduction in LDL-C. Thus the efficacy and cost data did not reflect the algorithm. The Panel ruled that the document was misleading in this regard in breach of Clause 7.2.

The Panel noted that a bar chart compared the percentage reduction in LDL-C from baseline for simvastatin (10-80mg), rosuvastatin (10-40mg) and atorvastatin (10-80mg). It appeared that if a greater percentage reduction was required than was possible with simvastatin 80mg (approximately -45%) then patients would have to receive either rosuvastatin (20 or 40mg) or atorvastatin (40 or 80mg). This was followed by the Moon and Bogle quotation then the claim 'Rosuvastatin, at a start dose of 5 or 10mg, is the most cost effective choice after simvastatin'. Given the content of the bar chart and the positioning of the claim the Panel considered that the claim was misleading as the cost efficacy of the 5mg and 10mg doses were irrelevant given that usually higher doses would be needed. In addition the bar chart did not give any indication of the LDL-C reduction from baseline for the 5mg dose. A breach of Clause 7.2 was ruled.

Below the claim were two tables of data showing the cost per 1% LDL-C reduction for rosuvastatin (5-40mg) and atorvastatin (10-80mg). It was stated that the cost was based on pack sizes of 28 tablets. Given that the cost of 28 x 40mg rosuvastatin was £29.69 and it lowered LDL-C from baseline by 55% the cost per percentage LDL-C reduction was stated as 53 pence. This cost, however, took no account of the fact that the SPC recommended specialist supervision when the 40mg dose was initiated. Further 40mg should only be used in high risk patients in whom routine follow-up would be performed. Such follow-up would add to the cost of therapy. In that regard the Panel considered that the data was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the bar chart which compared the percentage reduction in LDL-C from baseline showed results for rosuvastatin 10mg, 20mg and 40mg. It thus appeared that the lowest dose of rosuvastatin was 10mg which was not so. A 5mg dose was available which, according to the Crestor SPC, was recommended in, *inter alia*, patients >70 years or those with moderate renal impairment. Although a footnote to the bar chart stated 'For recommended start and maximum doses for individual patients,

please refer to SmPC', this did not, in the Panel's view, negate the otherwise misleading impression with regard to the availability of doses. A breach of Clause 7.2 was ruled.

The Panel noted that a cost comparison chart was on a page headed 'Prescribing statins' with a subheading 'Lipid Lowering Drugs – cost comparison'. The chart listed a number of lipid lowering agents and gave their cost for 28 days' treatment. The least expensive option was simvastatin 20mg (£1.71) and the most expensive was colestipol 20mg at £56.19. Three agents were highlighted – simvastatin 40mg (£3.89), rosuvastatin 10mg (£18.03) and atorvastatin 40mg, 80mg (£28.21). The Panel noted that, according to the bar chart on the previous page which showed the percentage reduction in LDL-C from baseline, simvastatin 40mg would lower LDL-C by up to approximately -38%, rosuvastatin by up to -45% and atorvastatin 80mg by up to -50%. In terms of LDL-C lowing efficacy these three agents were thus not equivalent. The Panel considered, however, by highlighting these three medicines/doses, readers would assume that they were therapeutically equivalent which was not so. The footnote 'Doses given do not imply therapeutic equivalence' did not negate the impression given. The Panel considered that cost comparison chart was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the cost comparison chart was not limited to statins; it was unclear as to the basis on which products had been chosen. Rosuvastatin had been included but only at doses of 10mg, 20mg and 40mg. The cost of rosuvastatin 5mg was not stated. Pravastatin was included but only at a dose of 20mg although the recommended dose range was 10-40mg daily. The Code stated that valid price comparisons could only be made where like was compared with like The basis of the cost comparison shown in the PCT statins guidelines was unclear and in this regard the document was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect no health but would save £1.1bn over five years…' was referenced to Moon and Bogle. Pfizer had submitted that there had been some debate about the assumptions made by the authors but had not provided any detail in that regard. There was no response from AstraZeneca. Nonetheless the Panel considered that not everyone who currently took 20mg atorvastatin would be suitable to change to simvastatin 40mg. In that regard the Panel noted that the percentage reduction in LDL-C from baseline for the two products was shown in the document at issue as approximately -41% and -38% respectively. Thus some patients on atorvastatin 20mg might fail to reach lipid targets if they were switched to simvastatin 40mg. On the information provided the Panel considered that the single, short quotation from Moon and Bogle might be misleading in this regard but nonetheless it did not disparage atorvastatin as alleged and so no breach of Clause 8.1 was ruled.

The Panel noted its rulings above. The Panel considered that the guideline failed to present a balanced view of the risk/benefit ratio of any treatment as alleged. A breach of Clause 7.10 was ruled.

3 Alleged breaches of Clauses 2 and 9.1

COMPLAINT

Pfizer alleged that the degree of potential confusion over the true content of the two items considered above, the similarity in nature of the breaches contained within and the short time-period over which they were produced suggested consistent shortfalls within AstraZeneca and, as such, breaches of Clauses 9.1 and 2.

RESPONSE

AstraZeneca did not consider that the circumstances set out above warranted a ruling of a breach of Clause 9.1 and of Clause 2 of the Code solely in relation to the PCT guidelines and did not consider that Pfizer was alleging this in any event. The company did not accept that there had been any breach of the Code in relation to the supplement in The Pharmaceutical Journal therefore it did not consider a ruling of the breach of Clause 2 based on multiple, cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time was justified.

In any event, the facts behind the supplement in The Pharmaceutical Journal were substantially similar to those concerning Cases AUTH/1951/2/07 to AUTH/1955/2/07. Since these cases were the subject of an appeal it would be inappropriate and premature to conclude a definitive ruling of a breach of Clause 2 for this Case AUTH/1977/3/07.

AstraZeneca's internal procedures in relation to promotional copy-review and approval were an integral part of the company's commercial activities and reflected an intention to ensure the highest ethical standards in its communications with the health professionals and other external customers. The company viewed it's obligations to the Code as an essential part of this activity.

AstraZeneca did not therefore accept that there had been breaches of Clauses 2 and 9.1.

PANEL RULING

The Panel noted that AstraZeneca had failed to recognise that the document placed in The Pharmaceutical Journal was, in effect, promotional material for Crestor. Similarly the PCT guidelines document had been entered into the company's copy approval system in such a way that the intent of the originator had either not been apparent or had been misinterpreted by the signatories. The Panel considered that such flaws in the copy approval system, highlighted by the generation of both documents, were unacceptable. High standards had

not been maintained. A breach of Clause 9.1 was ruled.

The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in both documents, neither referred to the requirements in the SPC with regard to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in this regard, the two documents had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its rulings above and in accordance with Paragraph 7.1 of the Constitution and Procedure decided that if there was subsequently an appeal by AstraZeneca relating to the PCT Prescribing Statins guideline document it would require AstraZeneca to suspend the use of the document pending the final outcome. The supplement from The Pharmaceutical Journal was already the subject of a forthcoming appeal.

The Panel considered that this case highlighted an apparent lack of control in AstraZeneca's copy approval system. Furthermore the Panel was extremely concerned that when it had asked the company for further information about the PCT guidelines document, AstraZeneca had submitted a wholly different response to the Authority from its first one. In its second response the company had submitted that it had now had the opportunity to undertake a full investigation into this complaint, including conversations with the relevant personnel. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007. AstraZeneca's second response to the Authority differed markedly from the first. This was unacceptable. Self-regulation depended upon companies investigating matters fully at the outset and submitting full and frank responses both in inter-company correspondence and to the Authority. The Panel also noted AstraZeneca's dismissal of questions relating to the content of the PCT guidelines document.

Overall, the Panel was extremely concerned about AstraZeneca's procedures with regard to the Code including its incorrect initial responses and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that AstraZeneca had accepted all of the rulings regarding the piece which had been distributed with The Pharmaceutical Journal; rather than being a supplement in The Pharmaceutical Journal, as described by AstraZeneca, the Appeal Board had previously decided in Cases AUTH/1951/2/07 to AUTH/1955/2/07 that the piece was a paid for insert in the journal not a supplement sponsored by The Pharmaceutical Journal. The Appeal Board had considered that the insert was promotional material for Crestor. The Appeal Board noted that it would consider the report on the basis of the information before it in the present case (Case AUTH/1977/3/07).

The Appeal Board noted from AstraZeneca that its erroneous belief that the PCT Prescribing Statins guidelines document was a PCT-generated document was solely based upon a verbal communication from the medical signatory responsible for the piece. The Appeal Board was concerned that there had been no follow up investigation or documentation sought to confirm whether this was correct. Had this been done it would have shown the communication was untrue. The Appeal Board also noted AstraZeneca's submission that there was inadequate communication between the field and head office about the PCT document. The Appeal Board was concerned that AstraZeneca had responded to both Pfizer in its inter-company correspondence and then to the Authority in its initial response to the complaint without adequate investigation. This was totally unacceptable. There was no documentation in the job bag to support PCT involvement with the generation of the guidelines. It appeared that only upon investigation of a request for further information by the Panel did AstraZeneca discover that its initial response was incorrect and so informed the Authority.

The Appeal Board noted that AstraZeneca had stated that the PCT Prescribing Statins guidelines document had been withdrawn on 1 March. However, the Appeal Board noted that an email timed at 16:36 on 1 March highlighted the requirements of the Code relevant to the delivery of the item but allowed continued use. The Appeal Board noted from AstraZeneca that despite this permitted use, due to continuing confusion about the item's use, verbal confirmation had been ascertained from the field force forum that the item had not been used beyond 1 March. The Appeal Board was concerned that the process for withdrawal of the item was uncertain. An email permitting use could not amount to effective withdrawal of use.

The Appeal Board noted the submission from AstraZeneca which accepted that errors had been made. AstraZeneca apologised for the errors and provided details of the corrective action it had taken.

The Appeal Board considered that effective and robust self-regulation was reliant upon companies making fully informed responses to complaints. AstraZeneca had not made sufficient investigations and as a result it had provided incorrect responses which was totally unacceptable. The Appeal Board considered this matter to be of the utmost seriousness.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of AstraZeneca's procedures in relation to the Code to be carried out by the Authority. On receipt of the audit report the Appeal

Board would decide whether any further action was required. In addition the Appeal Board decided, on the basis that it had not fully investigated the matter of the PCT Prescribing Statins guidelines when it responded to Pfizer and in its first response to the Authority, that AstraZeneca should be publicly reprimanded.

Upon receipt of the audit report, the Appeal Board considered that AstraZeneca should provide the Authority with a copy of its new standard operating procedures (SOPs). On the basis that the SOPs were provided and that the recommendations from the audit report were implemented the Appeal Board decided that no further action was required.

Complaint received	**16 March 2007**
Case completed	**21 June 2007**
Report to the Appeal Board	**19 July 2007**